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MOLECULAR AND ELECTRONIC MECHANISM IN THE CONTROL OF
NA(+) AND K(+) PERME. (U) PENNSYLVANIA HOSPITAL
PHILADELPHIA DEPT OF MOLECULAR BIOLOGY. G N LING

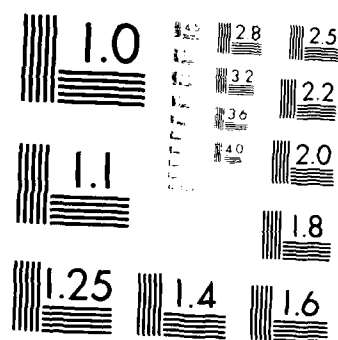
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12 PERSONAL AUTHOR(S) Gilbert N. Ling, Ph.D.				
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<p>Our objective is to investigate the control of cell membrane permeability to Na⁺, K⁺, and other ions by transmitters, drugs, and other biologically potent ligands: to extend and test a general electronic theory of the control of physiological activities.</p>				
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Principal Investigator: Gilbert N. Ling, Ph.D.

Contractor: Pennsylvania Hospital

Contract Title: "Molecular and Electronic Mechanism in the Control of Na^+ and K^+ Permeability of Excitable Cell Membrane by Ligand Binding on Receptor Sites" Codes
x/or
al

Start Date: 1 July 1985

Research Objective:

To investigate the control of cell membrane permeability to Na^+ , K^+ , and other ions by transmitters, drugs, and other biologically potent ligands: to extend and test a general electronic theory of the control of physiological activities.

Progress:

(Year 1 and 2): In 1962, a new theory of cell physiology called the association-induction (AI) hypothesis was published. As its title indicates, this theory can be roughly divided into two parts: "association" which describes, in time-space coordinates, the relationships among the three major components of the living matter: proteins, water, and ions; "induction" which describes in electronic terms the all-or-none shifts between resting and active physiological states brought on by controlling agents including transmitters, drugs, hormones, ATP, Ca^{++} , etc. Uninterrupted support of ONR (and NIH) for the last 25 years had made possible the verification of the essence of the association aspect of the new paradigm. The new ONR interest in the excitable "membrane physiology", guided by Dr. Martin Blank, gave impetus to new efforts to study the control mechanisms (which contributes to hopes that one day mankind may eventually through the development of rational drug therapy conquer the ever-mutating and ever-evolving lethal viruses like AIDS).

In the last two years we have made progress in two directions:

(1) To establish that electronic polarization or induction - which underlies the behaviors of all small organic molecules - also plays key roles in the behaviors of proteins and hence all living cells which are made of proteins (water and ions). More specifically, the secondary structures of proteins (i.e., the specific ways of folding) are predetermined by its primary structure (i.e., the nature and sequential order of the amino acid residues in the protein chain) - a fact known, but essentially unexplained - is now found explicable in terms of the inductive effect (see Publ. #1 - Ling, Physiol. Chem. Phys. and Med. NMR 18:3 (1986)).

(2) The key postulates of the theory of (the resting and) action potential which was first introduced in 1960, have been confirmed (though both the theory and its confirmation have been little known). These postulates include:

- (i) that during the initial phase of the action potential, the cell surface β - and γ -carboxyl groups undergo an increase of electron density or "c-value" (and a rise of pK_a values); and
- (ii) that such c-value changes occur in the same β - and γ -carboxyl groups. Using the multiple ion probe method, Ling and Fu have now obtained additional evidence that the cell surface β - and γ -groups of two types of living cells (frog skeletal muscle and frog ovarian

eggs) do indeed increase their c-value in response to interaction with a cardinal adsorbent, the drug, ouabain. Furthermore, ouabain consistently acts as an "electron donating cardinal adsorbent" (EDC) in its control of the cytoplasmic β - and γ -carboxyl groups (responsible for the bulk phase accumulation of alkali-metal ions); the cell surface β - and γ -carboxyl groups (that give rise to the resting potential); as well as the cell surface β - and γ -carboxyl groups (that mediate the traffic of K^+ , Na^+ , and other alkali-metal ions in and out of living cells) (Ms. #2).

Work Plan:

(Year 3): The success of the multiple ion probe method (Ms. #1 and 2) in detecting and in measuring both the direction and magnitude of the c-value changes of β - and γ -carboxyl groups in response to the binding of drugs or other ligands has opened the door toward further testing the hypothesis that alkaloids like veratridine and aconitine that can emulate the theoretical "gating particle" and generate a sustained cell membrane depolarization and activation like that seen transiently during an action potential is distinguished from effects of other non-activating EDC's (e.g., ouabain) in consequence of a much larger c-value increase created and the hypothesis that "channel blockers" (e.g., tetrodotoxin) may act by virtue of this opposing electronic effect on the β - and γ -carboxyl group as that giving rise to the rapid initial surge of inward Na^+ current; in other words, tetrodotoxin may act as an electron-withdrawing cardinal adsorbent (EWC). We also plan to see if we can study the effects of enough numbers of drugs, transmitters, and other cardinal adsorbents on the membrane permeability (and other related physiological manifestations) to test the hypothesis that all effective drugs, transmitters, and other cardinal adsorbents can be classified in two categories: EDC and EWC and that each cardinal adsorbent can produce a characteristic quantitatively similar c-value change on different parts of the living cell as our study of the cardiac glycoside has already demonstrated.

Publications:

Multiple supports from different grant-agencies have been vital to our operation. Our continued research and publications on cell water related subjects (after ONR support for work on cell water had ceased) was because 75% of our total current financial support is from the National Cancer Institute, under the title, "What Distinguishes Water in Normal and Cancer Cells?"

- * A. Book: "A Revolution in Physiology of the Living Cell: and Beyond" is a landmark volume chronicling work performed under both previous and present ONR contracts. It is in this volume (but not yet in the large volume, In Search of the Physical Basis of Life) that the completion of a revolution in cell physiology is fully described.

B. Publications in Print:

- * Publ. #1 - Ling, G. N., "The Role of Inductive Effect in the Determination of Protein Structure", Physiol. Chem. Phys. and Med. NMR 18:3 (1986)

Publ. #2 - Heidorn, D. B., Rorschach, H. E., Hazlewood, C. F., Ling, G. N., and Nicklow, R. M., "Neutron Scattering Studies of Water in Frog Muscle", Biophys. J. 49:92A (1986)

Publ. #3 - Ling, G. N., and Ochsenfeld, M. M., "Membrane Lipid Layer vs.

- * Polarized Water Dominated by Fixed Ions: A Comparative Study of the

Effects of Three Macrocyclic Ionophores on the K^+ Permeability of Frog Skeletal Muscle, Frog Ovarian Eggs, and Human Erythrocytes", Physiol. Chem. Phys. and Med. NMR 18:109 (1986)

- * Publ. #4 - Ling, G. N., "Cooperative Interaction Among Surface β - and γ -carboxyl Groups Mediating the Permeation of Ions Into Frog Muscle Cells", Physiol. Chem. Phys. and Med. NMR 18:125 (1986)

Publ. #5 - Ling, G. N., Reid, C., and Murphy, R. C., "Are the Proteins in Malignant Cancer Cells of Diverse Origin Similar or Different?" Physiol. Chem. Phys. and Med. NMR 18:147 (1986)

Publ. #6 - Ling, G. N., "A Theory of the Water Contents of Living Cells in Solutions Containing Different Concentrations of Permeant Solutes" (short note) Physiol. Chem. Phys. and Med. NMR 18:131 (1986)

Publ. #7 - Ling, G. N., "The Origin of Cellular Electrical Potentials" in: Modern Bioelectrochemistry, eds. F. Gutman and H. Keyzer, Plenum Press, New York, 1985

Publ. #8 - Ling, G. N., "Experimental Confirmation of the Polarized Multi-layer Theory of Cell Water Including Data That Lead to an Improved Definition of Colloids" in: Water and Ions in Biological Systems, eds. A. Pullman, V. Vasilescu, and L. Packer, Plenum Press, New York and London, 1985

Publ. #9 - Ling, G. N., "In Search of the Physical Basis of Life" in: Advances in Physiological Research, eds. H. McLennan, J. R. Ledsome, C. H. S. McIntosh, and D. R. Jones, Plenum Press, New York, p. 469-492 (1986)

C. Manuscripts in Various Stages of Publication But Not Yet in Print:

- * Ms. #1 - Ling, G. N., and Fu, Y., "An Electronic Mechanism in the Action of Drugs, and Other Cardinal Adsorbents. I. Effect of the Cardiac Glycoside, Ouabain, on the Relative Affinities of the Frog Muscle Cell Surface β - and γ -carboxyl Groups for K^+ , Na^+ , and Other Ions" (in press), Physiol. Chem. Phys. and Med. NMR

- * Ms. #2 - Ling, G. N., and Fu, Y., "An Electronic Mechanism in the Action of Drugs, and Other Cardinal Adsorbents. II. Effect of Ouabain on the Relative Affinities for Li^+ , Na^+ , K^+ , and Rb^+ of Surface Anionic Sites that Mediate the Entry of Cs^+ into Frog Ovarian Eggs" (accepted for publication), Physiol. Chem. Phys. and Med. NMR

Ms. #3 - Ling, G. N., "Cell Volumes and Water Contents of Frog Muscles in Solutions of Permeant Sugars and Sugar Alcohols" (in press), Physiol. Chem. Phys. and Med. NMR

- * Ms. #4 - Ling, G. N., "On the Large Error Introduced in the Estimate of the Density of Membrane Pores from Permeability Measurements when Diffusion in 'Unstirred Layer' within the Cells is Disregarded" (in press), Physiol. Chem. Phys. and Med. NMR

Ms. #5 - Ling, G. N., and Ochsenfeld, M. M., "Studies on the Physical State of Water in Living Cells and Model Systems. VI. Concentration-dependent Sustained Volume Changes of Dialysis Sacs Containing Aqueous Solution of

* These publications or manuscripts are primarily supported by ONR contract and/or are of direct relevance to the ONR-supported program.

Native and Denatured Protein, Gelatin, and Oxygen-containing Polymers Immersed in Solutions of Na Salt and of Sugar and Sugar Alcohol" (in press)
Physiol. Chem. Phys. and Med. NMR

Ms. #6 - Ling, G. N., "Studies on the Physical State of Water in Living Cells and Model Systems. VII. Exclusion of Sugars and Sugar Alcohols from the Water in Sulfonate Ion Exchange Resins: The 'Size Rule'" (in press)
Physiol. Chem. Phys. and Med. NMR

Ms. #7 - Ling, G. N., and Hu, W. X., "Studies on the Physical State of Water in Living Cells and Model Systems. VIII. Water Vapor Sorption on Proteins and Oxygen-containing Polymers at Physiological Vapor Pressures: Presenting a New Method for the Study of Vapor Sorption at Close To and Including Saturation" (in press) Physiol. Chem. Phys. and Med. NMR

Ms. #8 - Ling, G. N., "Do We Need a New View of the Living Cell" The Physical Aspect of the Living Cell, Eugene Ernst Memorial Symposium, July 3-5, 1986, Pecs, Hungary (accepted for publication)

Ms. #9 - Ling, G. N., "The Association-Induction Hypothesis and Life" Second European Congress on Cell Biology, July 6-11, 1986, Budapest, Hungary (accepted for publication)

Ms. #10 - Ling, G. N., "A Physical Theory of the Living State: Application to Water and Solute Distribution, SEM Conf., May 4-5, 1987, Hamilton, Ontario (accepted for publication)

Ms. #11 - Ling, G. N., "Solute Exclusion by Polymer and Protein-Dominated Water: Correlation with Results of NMR and Calorimetric Studies and Their Significance Toward the Understanding of the Physical State of Water in Living Cells" (accepted for publication)

Training Activities

Sharyn Horowitz, a highly motivated honor student, worked this summer at the laboratory on a volunteer basis.

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INVESTIGATORS

Dr. William E. Brownell
Department of Otolaryngology-HNS
Johns Hopkins University
School of Medicine
720 Rutland Avenue
Baltimore, MD 21205

Dr. Marco Colombini
Department of Zoology
University of Maryland
College Park, MD 20742

Dr. D. W. Deamer
Department of Zoology
University of California
Davis, CA 95616

Dr. Edward A. Dratz
Department of Chemistry
Montana State University
Bozeman, MT 59717

Dr. Harvey M. Fishman
Department of Physiology and
Biophysics
University of Texas Medical Branch
Galveston, TX 77550

Dr. Sol M. Gruner
Department of Physics
Jadwin Hall
Princeton University
P. O. Box 708
Princeton, NJ 08544

Dr. Felix T. Hong
Department of Physiology
Wayne State University
540 E. Canfield Avenue
Detroit, MI 48201

Dr. Huey W. Huang
Department of Physics
Rice University
Houston, TX 77001

Dr. Gilbert Ling
Pennsylvania Hospital
Eighth and Spruce Streets
Philadelphia, PA 19107

Dr. Israel R. Miller
The Weizmann Institute of Science
Rehovot 76100

Dr. V. Adrian Parsegian
Laboratory of Chemical Biology,
NIADDK
Room 9N-307
Building 10
Bethesda, MD 20892

Dr. David S. Perlin
Department of Biochemistry
Public Health Research Institute
455 First Avenue
New York, NY 10016

Dr. H. Gilbert Smith
EG & G Mason Research Institute
57 Union Street
Worcester, MA 01608

Dr. Michael E. Starzak
Department of Chemistry
State University of New York
Binghamton, NY 13901

Dr. H. Ti Tien
Department of Physiology
Membrane Biophysics Laboratory
Michigan State University
East Lansing, MI 48824

Dr. Tian Y. Tsong
Department of Biological Chemistry
Johns Hopkins University
School of Medicine
725 N. Wolfe Street
Baltimore, MD 21205

Dr. Petr Vanysek
Department of Chemistry
Northern Illinois University
De Kalb, IL 60115

Dr. Howard Wachtel
Depart. of Electrical & Computer Eng.
University of Colorado, Campus Box 425
Boulder, CO 80309

Dr. James C. Weaver
Div. Health Sciences & Technology
Room 20A-128
Massachusetts Institute of Tech.
Cambridge, MA 02139

Dr. George S. Wilson
Department of Chemistry
University of Kansas

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ADMINISTRATORS

Dr. Jeannine A. Majde, Code 1141SB (2 copies)
Program Manager, Systems Biology
Office of Naval Research
800 N. Quincy Street
Arlington, VA 22217-5000

Dr. Robert J. Nowak, Code 1113ES
Scientific Officer, Electrochemical
Sciences
Office of Naval Research
800 N. Quincy Street
Arlington, VA 22217-5000

Dr. Martin Blank, Scientific Officer
Department of Physiology
Columbia University College of Physicians
and Surgeons
630 West 168th Street
New York, NY 10032

Program Manager
Biological/Human Factors Division
Code 125
Office of Naval Research
800 N. Quincy Street
Arlington, VA 22217-5000

Administrator (2 copies) (Enclose DTIC Form 50)
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